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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,574	07/20/2001	Frank A. Skraly	MBX 039	2982

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EXAMINER	
PAK, YONG D	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 02/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/909,574	**Applicant(s)** SKRALY ET AL.	
	Examiner Yong D. Pak	**Art Unit** 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 December 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *21 December 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-4 and 6-10*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

ADVISORY ACTION

Response to Arguments

The amendment filed on December 21, 2005 under 37 CFR 1.116 in reply to the final rejection has been considered and has been entered but is not deemed to place the application in condition for allowance because: the request for consideration does not overcome the rejection of claims 1-4 and 6-10 under 35 U.S.C. 112, 1st paragraph, as discussed below.

Claims 1-4 and 6-10 are pending and are under consideration.

Claim Rejections - 35 USC § 112

Claims 1-4 and 6-10 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that since the claims recite that diol oxidoreductase and aldehyde dehydrogenase expressed by the organisms can convert diols into hydroxyalkanoate monomers, the claims are no longer drawn to diol oxidoreductase or aldehyde dehydrogenase having any structure. Examiner respectfully disagrees. It is unclear how this limitation describes the structure of the enzymes. Further, while it is

true that the claims are now drawn to a method of using diol oxidoreductase and aldehyde dehydrogenase expressed by the organisms which can convert diols into hydroxyalkanoate monomers, the claims remain drawn to a method of using a genus of diol oxidoreductase and aldehyde dehydrogenase having any structure. Therefore, contrary to applicant's arguments, one of skill in the art would not recognize that the applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus of aldehyde dehydrogenase and diol oxidoreductase. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a

genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genus of diol oxidoreductase and genus of aldehyde dehydrogenase include species which are widely variant in structure and substrate specificity. As such, the disclosure solely generic functional features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus.

Applicants also argue that the written description only requires proof that one of ordinary skill in the art would or did make and use the invention as described in the application and that since the instant specification provides not only representative materials from a broad spectrum of enzymes and substrates, but actual working examples, applicants have complied with the written description requirement. Examiner respectfully disagrees. The claims are not limited to specific enzymes taught in the specification, but the claims are drawn to a method of making polyhydroxyalkanoates from diols using a genus comprising any diol oxidoreductase that comprising of species that are structurally unrelated and utilize substrates unrelated to the diols listed above (See ExPASy database: diol oxidoreductase). Similarly, the claims are also drawn to a method of making polyhydroxyalkanoates from diols using a genus comprising any aldehyde dehydrogenase comprising of species that are structurally unrelated and utilize substrates unrelated to the diols listed above (see ExPASy database: aldehyde dehydrogenase). Therefore, the specification fails to describe a representative species of the genus of diol oxidoreductase, genus of aldehyde dehydrogenase and genus of diols used by a genus of plants to produce hydroxyalkanoates.

Applicants also argue that the Examiner is confusing the requirement for claiming the enzymes per se, rather than a method of use that utilizes enzymes having a defined specificity. Examiner respectfully disagrees. In order to practice the invention, one having ordinary skill in the art must select and identify the recited enzymes. However, the specification fails to provide sufficient guidance on this matter. **When there is substantial variation within the genus,** the genus comprising any diol oxidoreductase and the genus comprising any aldehyde dehydrogenase used in the method**, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

Applicants also argue that the specification and art describes how to isolate genes encoding aldehyde dehydrogenase and diol oxidoreductase from other organisms and therefore, applicants have complied with the written description requirement. Examiner respectfully disagrees. Even though some members of the genus of diol oxidoreductase and genus of aldehyde dehydrogenase genes were known in the art, neither art or the specification describes a method of producing polyhydroxyalkanoates using any diol oxidoreductase and any aldehyde dehydrogenase which are active in bacteria and plants by converting any diols into the recited hydroxyalkanoate monomers. Further, neither art nor specification describes a method of producing polyhydroxyalkanoates in any plants. Production of

polyhydroxyalkanoates in plants is limited. Art teaches that production of polyhydroxyalkanoates in plants is complicated because metabolism in plants is compartmentalized (Huisman et al. – form PTO-1449).

Hence the rejection is maintained.

Claims 1-4 and 6-10 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing polyhydroxyalkanoates from hydroxyalkanoates in bacteria by converting 1,6-hexanediol, 1,5-pentaediol, 1,4-butanediol, 1,3-propanediol, 1,2-ethanediol or 1,2-propanediol to its corresponding hydroxyalkanote using an aldehyde dehydrogenase (aldH) from *E. coli* and a 1,3-propanediol oxidoreductase (dhaT) from *K. pneumoniae,* does not reasonably provide enablement for a method of producing polyhydroxyalkanoates from hydroxyalkanoates using any or all diol oxidoreductases, any or all aldehyde dehydrogenases by converting any diols to hydroxyalkanoates in any plants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the specification and the prior art discloses organisms that can be used to produce polyhydroxyalkanoates, diols that may be utilized to form the claimed polyhydroxyalkanoate monomers and diol oxidoreductases and aldehyde

dehydrogenases used to convert diols into hydroxyalkanoate monomers and since methods for cloning genes encoding the above enzymes are well known and such methods are described in the specification, other aldehyde dehydrogenase and diol oxidoreductase can be cloned without undue experimentation. Examiner respectfully disagrees. The claims encompass converting any diols into the recited hydroxyalkanoate monomers using any diol oxidoreductase and any aldehyde dehydrogenase in any plant. Even though some members diol oxidoreductase and aldehyde dehydrogenase were known in the art, neither art or the specification describes a method of producing polyhydroxyalkanoates using any diol oxidoreductase and aldehyde dehydrogenase by converting any diols into the recited hydroxyalkanoate monomers. Further, neither art nor specification describes a method of producing polyhydroxyalkanoates in any plants. Production of polyhydroxyalkanoates in plants is limited. Art teaches that production of polyhydroxyalkanoates in plants is complicated because metabolism in plants is compartmentalized (Huisman et al. – form PTO-1449).

Applicants also argue that "the test for undue experimentation is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction win which the experimentation should proceed to able the determination of how to practice a desired embedment of the invention claimed". In the instant application, there is a considerable amount of experimentation which is not merely routine and the specification does not provide a reasonable amount of guidance with respect to the direction win which the experimentation should proceed. As

discussed above, the specification does not describe a method of producing polyhydroxyalkanoates using any diol oxidoreductase and aldehyde dehydrogenase by converting any diols into the recited hydroxyalkanoate monomers. Further, the specification does not describe a method of producing polyhydroxyalkanoates in any plants. Production of polyhydroxyalkanoates in plants is limited. Art teaches that production of polyhydroxyalkanoates in plants is complicated because metabolism in plants is compartmentalized (Huisman et al. – form PTO-1449).

Applicants also argue that there is no legal requirement that all of the enzymes within the scope of the claims convert the diols to their corresponding hydroxyalkanoate monomers for the enzymes to have the specified utility since "even if some of the claimed combinations were inoperative, the claims are not necessarily invalid" and it would only take routine experimentation to identify other aldehyde dehydrogenase and diol oxidoreductase that can convert the diols into their corresponding hydroxyalkanoates. Examiner respectfully disagrees. As discussed above, it would require undue experimentation of the skilled artisan to determine which specific set of enzymes from among the extremely large groups of enzymes as encompassed by the claims do actually work in order to practice the claimed method, which encompasses converting any diols into the recited hydroxyalkanoate monomers using any diol oxidoreductase and any aldehyde dehydrogenase in any plant. Also, according to the quote of the Federal Circuit cited by applicants, "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be

invalid." In the instant application, the number of inoperative combinations becomes signification and forces one of ordinary skill in the art to experiment unduly to practice the claimed invention because, as discussed above, it would require undue experimentation of the skilled artisan to determine which specific set of enzymes from among the extremely large groups of enzymes as encompassed by the claims do actually work in order to practice the claimed method, which encompasses converting any diols into the recited hydroxyalkanoate monomers using any diol oxidoreductase and any aldehyde dehydrogenase in any plant.

Applicants point to portions of the specification which enables one having ordinary skill in the art to select an appropriate aldehyde dehydrogenase or diol oxidoreductase or use in the claimed methods. Examiner respectfully disagrees. The portions of the specification pointed out by applicants teach only a few bacterial 1,3-propanediol oxidoreductase and that aldehyde dehydrogenases "are so numerous and varied". As discussed in the rejection, many different oxidoreductase from the family of diol dehydrogenase are known and many different dehydrogenase from the family of aldehyde dehydrogenases are known (see ExPASY database: aldehyde dehydrogenase and ExPASY database: diol oxidoreductase). "aldehyde dehydrogenase" and "diol oxidoreductase" include enzymes that are unrelated to converting diols into substrates for polyhydroxyalkanoate synthesis. Therefore, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of diol dehydrogenase, aldehyde dehydrogenase and diols broadly encompassed by the claims and undue

experimentation in identifying aldehyde dehydrogenase and diol oxidoreductase that can convert the diols into their corresponding hydroxyalkanoates.

Applicants also argue that Examiner has failed to provide any evidence to contradict applicant's evidence supporting enablement of the claims and that this is legal error. Examiner respectfully disagrees. MPEP states that the determination, of whether the claimed invention is enabled, "should always be based on the weight of all the evidence", which Examiner has done. There is no requirement that Examiner must rebut applicant's evidence by evidence. To establish and support a *prima facie* case of lack of enablement, specific technical reasons are sufficient (MPEP 2164.04).

Applicants also argue that there is no legal requirement to prove enablement for each and every species that may fall within the scope of the claims and the claims do not encompass enzyme that would not work and one of ordinary skill in the art would not select an enzyme that cannot perform this function. Examiner respectfully disagrees. While it is true that the claims are now drawn to a method of using diol oxidoreductase and aldehyde dehydrogenase expressed by the organisms which can convert diols into hydroxyalkanoate monomers, it would require undue experimentation of the skilled artisan to practice the claimed method, which encompasses converting any diols into the recited hydroxyalkanoate monomers using any diol oxidoreductase and any aldehyde dehydrogenase in any plant. As discussed above, it would require undue experimentation of the skilled artisan to determine which specific set of enzymes from among the extremely large groups of enzymes as encompassed by the claims do actually work in order to practice the claimed method, which encompasses converting

any diols into the recited hydroxyalkanoate monomers using any diol oxidoreductase and any aldehyde dehydrogenase in any plant. Also, according to the quote of the Federal Circuit cited by applicants, "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." In the instant application, the number of inoperative combinations becomes signification and forces one of ordinary skill in the art to experiment unduly to practice the claimed invention because, as discussed above, it would require undue experimentation of the skilled artisan to determine which specific set of enzymes from among the extremely large groups of enzymes as encompassed by the claims do actually work in order to practice the claimed method, which encompasses converting any diols into the recited hydroxyalkanoate monomers using any diol oxidoreductase and any aldehyde dehydrogenase in any plant.

Hence the rejection is maintained.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Manjunath Rao
Primary Patent Examiner 1652